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(54) Title: CO-ADMINISTRATION OF PERIFOSINE WITH CHEMOTHERAPEUTICS

(57) Abstract: The present invention is directed to methods of treating cancer by co-administration of perifosine and a second chemotherapeutic agent, which second chemotherapeutic agent includes, but is not limited to, paclitaxel, docetaxel, gemcitabine and trastuzumab.

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CO-ADMINISTRATION OF PERIFOSINE WITH CHEMOTHERAPEUTICS

The present application claims benefit under 35 U.S.C. § 119(e) of U.S. Provisional Application No. 60/648,080 filed January 28, 2005, the disclosure of which is incorporated by reference herein in its entirety.

1. FIELD OF THE INVENTION

The present invention is directed to methods of treating cancer by co-administration of perifosine and a second chemotherapeutic agent, which second chemotherapeutic agent includes, but is not limited to, paclitaxel, docetaxel, gemcitabine and trastuzumab.

2. BACKGROUND OF THE INVENTION

Perifosine (1,1-dimethyl-4[[(octadecyloxy)hydroxyphosphinyl]oxy]-piperidinium inner salt, is a synthetic, substituted heterocyclic alkylphospholipid, structurally related to miltefosine (NSC 60558, D-18506). The anti-tumor activity of miltefosine was initially evaluated in the 1980's, and it is licensed in Europe as a topical application for the treatment of patients with cutaneous metastases from breast cancer. It is also used in an oral formulation to treat leishmaniasis. However, because its only major toxicities are gastrointestinal and this was thought be a local rather than a central effect of the drug, numerous analogues were developed to see if a less toxic analogue could be identified.

Perifosine was identified as a potentially active and better tolerated analog of miltefosine. Its spectrum of activity across the NCI 60 cell line screen was very similar to miltefosine (Pearson correlation coefficient = 0.817). Both miltefosine and perifosine had very unique patterns of *in vitro* cell growth inhibition, unlike any "standard" chemotherapeutic agent. Perifosine has been shown to be more active and better tolerated than miltefosine in preclinical models (Hilgard *et al.*, 1997, Eur. J Cancer 33(3):442-446). Perifosine exhibited marked activity in animal and human tumor cell lines resistant to standard chemotherapeutic agents with relative sparing of normal cells, including macrophages and bone marrow cells.

Citation or identification of any reference in Section 2 or in any other section of this application shall not be construed as an admission that such reference is available as prior art to the present invention.

3. SUMMARY OF THE INVENTION

The present invention is directed to a method for treating solid tumors in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of perifosine and a second chemotherapeutic agent. In another embodiment, the present invention is directed to a method for inhibiting growth of solid tumors in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of perifosine and a second chemotherapeutic agent. In yet another embodiment, the present invention is directed to a method for inducing tumor regression, *e.g.*, tumor mass reduction, in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of perifosine and a second chemotherapeutic agent.

In yet another embodiment, the present invention is directed to a method for treating solid tumor invasiveness or symptoms associated with such tumor growth in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of perifosine and a second chemotherapeutic agent. In yet another embodiment, the present invention is directed to a method for preventing metastatic spread of tumors or for preventing or inhibiting growth of micro-metastases in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of perifosine and a second chemotherapeutic agent. The present invention also provides a method for the treatment of a disease associated with deregulated angiogenesis in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of perifosine and a second chemotherapeutic agent. The present invention also provides a method for inhibiting or controlling deregulated angiogenesis in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of perifosine and a second chemotherapeutic agent.

The present invention also provides a method for enhancing the activity of a chemotherapeutic agent or for overcoming resistance to a chemotherapeutic agent in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of perifosine and a second chemotherapeutic agent, either concomitantly or sequentially with said chemotherapeutic agent. In yet another embodiment, the present invention is directed to a method for treating post-transplant lymphoproliferative disorders

or a lymphatic cancer, *e.g.*, for treating tumor invasiveness or symptoms associated with such tumor growth in a subject in need thereof, comprising co-administering to said subject, concomitantly or in sequence, perifosine and a second chemotherapeutic agent.

4. DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to a method for treating solid tumors in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of perifosine and a second chemotherapeutic agent.

In another embodiment, the present invention is directed to a method for inhibiting growth of solid tumors in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of perifosine and a second chemotherapeutic agent.

In yet another embodiment, the present invention is directed to a method for inducing tumor regression, *e.g.*, tumor mass reduction, in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of perifosine and a second chemotherapeutic agent.

In yet another embodiment, the present invention is directed to a method for treating solid tumor invasiveness or symptoms associated with such tumor growth in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of perifosine and a second chemotherapeutic agent.

In yet another embodiment, the present invention is directed to a method for preventing metastatic spread of tumors or for preventing or inhibiting growth of micro-metastases in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of perifosine and a second chemotherapeutic agent.

As used herein, "solid tumors" are meant tumors and/or metastasis (where ever located) other than lymphatic cancer, *e.g.*, brain and other central nervous system tumors (*e.g.*, tumors of the meninges, brain, spinal cord, cranial nerves and other parts of central nervous system, *e.g.*, glioblastomas or medulla blastomas); head and/or neck cancer; breast tumors; circulatory system tumors (*e.g.*, heart, mediastinum and pleura, and other intrathoracic organs, vascular tumors and tumor-associated vascular tissue); excretory system tumors (*e.g.*, kidney, renal pelvis, ureter, bladder, other and unspecified urinary organs); gastrointestinal tract tumors (*e.g.*, esophagus, stomach, small intestine, colon, colorectal, rectosigmoid junction, rectum, anus and anal canal), tumors involving the liver and intra-hepatic bile ducts, gall bladder, other and unspecified parts of binary tract, pancreas, other and digestive organs); head and neck; oral cavity (lip, tongue, gum, floor of

mouth, palate, and other parts of mouth, parotid gland, and other parts of the salivary glands, tonsil, oropharynx, nasopharynx, pyriform sinus, hypopharynx, and other sites in the lip, oral cavity and pharynx); reproductive system tumors (*e.g.*, vulva, vagina, Cervix uteri, Corpus utcri, uterus, ovary, and other sites associated with female genital organs, placenta, penis, prostate, testis, and other sites associated with male gcnital organs); respiratory tract tumors (*e.g.*, nasal cavity and middle ear, accessory sinuses, larynx, trachea, bronchus and lung, *e.g.*, small cell lung cancer or non-small cell lung cancer); skeletal system tumors (*e.g.*, bone and articular cartilage of limbs, bone articular cartilage and other sites); skin tumors (*e.g.*, malignant melanoma of the skin, non-melanoma skin cancer, basal cell carcinoma of skin, squamous cell carcinoma of skin, mesothelioma, Kaposi's sarcoma); and tumors involving other tissues including peripheral nerves and autonomic nervous system, connective and soft tissue, retroperitoneum and peritoneum, eye and adnexa, thyroid, adrenal gland and other endocrine glands and related structures, secondary and unspecified malignant neoplasm of lymph nodes, secondary malignant neoplasm of respiratory and digestive systems and secondary malignant neoplasm of other sites.

Where hereinbefore and subsequently a tumor, a tumor disease, a carcinoma or a cancer is mentioned, metastasis in the original organ or tissue and/or in any other location is implied alternatively or in addition, whatever the location of the tumor and/or metastasis.

The present invention also provides a method for the treatment of a disease associated with deregulated angiogenesis in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of perifosine and a second chemotherapeutic agent.

The present invention also provides a method for inhibiting or controlling deregulated angiogenesis in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of perifosine and a second chemotherapeutic agent.

The present invention also provides a method for enhancing the activity of a chemotherapeutic agent or for overcoming resistance to a chemotherapeutic agent in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of perifosine and a second chemotherapeutic agent, either concomitantly or sequentially with said chemotherapeutic agent. In a particular aspect, the chemotherapeutic agent is an inhibitor of signal transduction pathways directed either against host cells or processes involved in tumor formation and/or metastases formation or utilized by tumor cells for proliferation, survival, differentiation or development of drug resistance. Examples

of diseases associated with deregulated angiogenesis include without limitation, *e.g.*, ncoplastic diseases, *e.g.*, solid tumors. Angiogenesis is regarded as a prerequisite for those tumors which grow beyond a certain diameter, *i.e.*, about 1-2 mm.

In yet another embodiment, the present invention is directed to a method for treating post-transplant lymphoproliferative disorders or a lymphatic cancer, *e.g.*, for treating tumor invasiveness or symptoms associated with such tumor growth in a subject in need thereof, comprising co-administering to said subject, concomitantly or in sequence, perifosine and a second chemotherapeutic agent.

As used herein, "lymphatic cancer" is meant to encompass tumors of blood and lymphatic system (*e.g.*, Hodgkin's disease, Non-Hodgkin's lymphoma, Burkitt's lymphoma, AIDS-related lymphomas, malignant immunoproliferative diseases, multiple myeloma and malignant plasma cell neoplasms, lymphoid leukemia, myeloid leukemia, acute or chronic lymphocytic leukemia, monocytic leukemia, other leukemias of specified cell type, leukemia of unspecified cell type, other and unspecified malignant neoplasms of lymphoid, haematopoletic and related tissues, for example diffuse large cell lymphoma, T-cell lymphoma or cutaneous T-cell lymphoma).

The second chemotherapeutic agent is meant to include chemotherapeutic agents, including but is not limited to, an aromatase inhibitor, an antiestrogen, an anti-androgen (especially in the case of prostate cancer) or a gonadorelin agonist, a topoisomerase I inhibitor or a topoisomerase II inhibitor, a microtubule active agent, an alkylating agent, an antineoplastic antimetabolite or a platin compound, a compound targeting/decreasing a protein or lipid kinase activity or a protein or lipid phosphatase activity, a further anti-angiogenic compound or a compound which induces cell differentiation processes, a bradykinin I receptor or an angiotensin II antagonist, a cyclooxygenase inhibitor, a bisphosphonate, a histone deacetylase inhibitor, a heparanase inhibitor (prevents heparan sulphate degradation), *e.g.*, PI-88, a biological response modifier, preferably a lymphokine or interferons, *e.g.*, interferon-gamma., an ubiquitination inhibitor, or an inhibitor which blocks anti-apoptotic pathways, an inhibitor of Ras oncogenic isoforms, *e.g.*, H-Ras, K-Ras or N-Ras, or a famesyl transferase inhibitor, e.g. L-744,832 or DK8G557, a telomerase inhibitor, *e.g.*, telomestatin, a protease inhibitor, a matrix metalloprotelnase inhibitor, a methionine aminopeptidase inhibitor, e.g. bengamide or a derivative thereof, or a proteosome inhibitor, *e.g.*, PS-341.

As used herein, "aromatase inhibitor" relates to a compound which inhibits the estrogen production, *i.e.*, the conversion of the substrates androstenedione and testosterone

to estrone and estradiol, respectively. The term includes, but is not limited to steroids, especially atamestane, exemestane and formestane and, in particular, non-steroids, especially aminoglutethimide, roglethimide, pyridoglutethimide, trilostane, testolactone, ketokonazole, vorozole, fadrozole, anastrozole and letrozole. Exemestane can be administered in the form as it is marketed under the trademark AROMASIN™. Formestane can be administered in the form as it is marketed under the trademark LENTARON™. Fadrozole can be administered in the form as it is marketed under the trademark AFEMA™. Anastrozole can be administered in the form as it is marketed under the trademark ARIMIDEX™. Letrozole can be administered in the form as it is marketed under the trademark FEMARA™ or FEMAR™. Aminoglutethimide can be administered in the form as it is marketed under the trademark ORIMETEN™. A combination of the invention comprising a chemotherapeutic agent which is an aromatase inhibitor is particularly useful for the treatment of hormone receptor positive tumors, *e.g.*, breast tumors.

As used herein, "antiestrogen" relates to a compound which antagonizes the effect of estrogens at the estrogen receptor level. The term includes, but is not limited to tamoxifen, fulvestrant, raloxifene and raloxifene hydrochloride. Tamoxifen can be administered in the form as it is marketed under the trademark NOLVADEX™. Raloxifene hydrochloride can be administered in the form as it is marketed under the trademark EVISTA™. Fulvestrant can be formulated as disclosed in U.S. Pat. No. 4,659,516 or it can be administered in the form as it is marketed under the trademark FASLODE™. A combination of the invention comprising a chemotherapeutic agent which is an antiestrogen is particularly useful for the treatment of estrogen receptor positive tumors, *e.g.*, breast tumors.

As used herein, "anti-androgen" relates to any substance which is capable of inhibiting the biological effects of androgenic hormones and includes, but is not limited to, bicalutamide (CASODEX™), which can be formulated, *e.g.*, as disclosed in U.S. Pat. No. 4,636,505. As used herein, "gonadorelin agonist" includes, but is not limited to, abarelix, goserelin and goserelin acetate. Goserelin is disclosed in U.S. Pat. No. 4,100,274 and can be administered in the form as it is marketed under the trademark ZOLADEX™. Abarelix can be formulated, *e.g.*, as disclosed in U.S. Pat. No. 5,843,901.

As used herein, "topoisomerase I inhibitor" includes, but is not limited to, topotecan, irinotecan, 9-nitrocamptothecin and the macromolecular camptothecin conjugate PNU-166148 (compound A1 in WO99/17804). Irinotecan can be administered in the form as it is marketed under the trademark CAMPTOSAR™. Topotecan can be administered in the form as it is marketed under the trademark HYCAMTIN™.

As used herein, "topoisomerase II inhibitor" includes, but is not limited to, the anthracyclines such as doxorubicin (including liposomal formulation, *e.g.*, CAELYX™), daunorubicin, epirubicin, idarubicin and nemorubicin, the anthraquinones mitoxantrone and losoxantrone, and the podophillotoxines etoposide and teniposide. Etoposide can be administered in the form as it is marketed under the trademark ETOPOPHOS™. Teniposide can be administered in the form as it is marketed under the trademark VM 26-BRISTOL™. Doxorubicin can be administered in the form as it is marketed under the trademark ADRIBLASTIN™. Epirubicin can be administered in the form as it is marketed under the trademark FARMORUBICIN™. Idarubicin can be administered in the form as it is marketed under the trademark ZAVEDOS™. Mitoxantrone can be administered in the form as it is marketed under the trademark NOVANTRON™.

As used herein, "microtubule active agent" relates to microtubule stabilizing and microtubule destabilizing agents including, but not limited to, taxanes, *e.g.*, paclitaxel and docetaxel, vinca alkaloids, *e.g.*, vinblastine, especially vinblastine sulfate, vincristine especially vincristine sulfate, and vinorelbine, discodermolides and epothilones and derivatives thereof, *e.g.*, epothilone B or a derivative thereof. Paclitaxel may be administered in the form as it is marketed under the trademark TAXOL™. Docetaxel can be administered in the form as it is marketed under the trademark TAXOTERE™. Vinblastine sulfate can be administered in the form as it is marketed under the trademark VINBLASTIN R.P.™. Vincristine sulfate can be administered in the form as it is marketed under the trademark FARMISTIN™. Discodermolide can be obtained, *e.g.*, as disclosed in U.S. Pat. No. 5,010,099.

As used herein, "alkylating agent" includes, but is not limited to, cyclophosphamide, ifosfamide, melphalan or nitrosourea (BCNU or Gliadel.TM.). Cyclophosphamide can be administered in the form as it is marketed under the trademark CYCLOSTIN™. Ifosfamide can be administered in the form as it is marketed under the trademark HOLOXAN™.

As used herein, "antineoplastic antimetabolite" includes, but is not limited to, 5-fluorouracil, capecitabine, gemcitabine, methotrexate and edatrexate. Capecitabine can be administered in the form as it is marketed under the trademark XELODA™. Gemcitabine can be administered in the form as it is marketed under the trademark GEMZAR™.

As used herein, "platin compound" includes, but is not limited to, carboplatin, cis-platin and oxaliplatin. Carboplatin can be administered in the form as it is marketed under the trademark CARBOPLAT™. Oxaliplatin can be administered in the form as it is marketed under the trademark ELOXATIN™.

As used herein, "compounds targeting/decreasing a protein or lipid kinase activity or further anti-angiogenic compounds" includes, but is not limited to, protein tyrosine kinase and/or serine and/or threonine kinase inhibitors or lipid kinase inhibitors, *e.g.*, compounds targeting, decreasing or inhibiting the activity of the epidermal growth factor family of receptor tyrosine kinases (EGFR, ErbB2, ErbB3, ErbB4 as homo- or heterodimers), the vascular endothelial growth factor family of receptor tyrosine kinases (VEGFR), the platelet-derived growth factor-receptors (PDGFR), the fibroblast growth factor-receptors (FGFR), the insulin-like growth factor receptor 1 (IGF-1 R), the Trk receptor tyrosine kinase family, the Axi receptor tyrosine kinase family, the Ret receptor tyrosine kinase, the Kit/SCFR receptor tyrosine kinase, members of the c-Abl family and their gene-fusion products (*e.g.*, BCR-Abl), members of the protein kinase C (PKC) and Raf family of serine/threonine kinases, members of the MEK, SRC, JAK, FAK, PDK or PI(3) kinase family, or of the PI(3)-kinase-related kinase family, and/or members of the cyclin-dependent kinase family (CDK) and anti-anglogenic compounds having another mechanism for their activity, *e.g.*, unrelated to protein or lipid kinase inhibition.

Compounds which target, decrease or inhibit the activity of VEGFR are compounds, proteins or antibodies which inhibit the VEGF receptor tyrosine kinase, inhibit a VEGF receptor or bind to VEGF, and are in particular those compounds, proteins or monoclonal antibodies generically and specifically disclosed in WO 98/35958, *e.g.*, 1-(4-chloroanilino)-4-(4-pyridylmethyl)phthalazine or a pharmaceutically acceptable salt thereof, *e.g.*, the succinate, or in WO 00/09495, WO 00/27820, WO 00/59509, WO 98/11223, WO 00/27819 and EP 0 769 947; those as described by M. Prewett *et al.*, 1991, Cancer Research 59:5209-5218, by F. Yuan *et al.*, 1996, Proc. Natl. Acad. Sci. USA, 93:14765-14770; Z. Zhu *et al.*, 1998, Cancer Res. 58:3209-3214, and by J. Mordenti *et al.*, 1999, Toxicologic Pathology, 27(1):14-21, 1999; in WO 00/37502 and WO 94/10202; Angiostatin™, described by M.S. O'Reilly *et al.*, 1994, Cell 79:315-328; Endostatin™, described by M.S. O'Reilly *et al.*, 1997, Cell 88:277-285; anthranilic acid amides; ZD4190; ZD6474; SU5416; SU6668; or anti-VEGF antibodies or anti-VEGF receptor antibodies, *e.g.*, RhuMab.

Compounds which target, decrease or inhibit the activity of the epidermal growth factor receptor family are especially compounds, proteins or antibodies which inhibit members of the EGF receptor tyrosine kinase family, *e.g.*, EGF receptor, ErbB2, ErbB3 and ErbB4 or bind to EGF or EGF related ligands, and are in particular those compounds, proteins or monoclonal antibodies generically and specifically disclosed in WO 97/02266, *e.g.*, in EP 0 564 409, WO 99/03854, EP 0520722, EP 0 566 226, EP 0 787 722, EP 0 837

063, U.S. Pat. No. 5,747,498, WO 98/10767, WO 97/30034, WO 97/49688, WO 97/38983 and, especially, WO 96/30347 (*e.g.*, compound known as CP 358774), WO 96/33980 (*e.g.*, compound ZD 1839) and WO 95/03283 (*e.g.*, compound ZM105180); *e.g.*, trastuzumab (Herpetin.sup.R), cetuximab, Iressa, OSI-774, CI-1033, EKB-569, GW-2016, E1.1, E2.4, E2.5, E6.2, E6.4, E2.11, E6.3 or E7.6.3.

Compounds which target, decrease or inhibit the activity of PDGFR also are compounds which inhibit the PDGF receptor, *e.g.*, a N-phcnyl-2-pyrimidine-amine derivative, *e.g.*, imatinib. Compounds which target, decrease or inhibit the activity of c-Abl family members and their gene fusion products include, *e.g.*, a N-phenyl-2-pyrimidine-amine derivative, *e.g.*, imatinib; PD180970; AG957; and NSC 680410. Compounds which target, decrease or inhibit the activity of protein kinase C, Raf, MEK, SRC, JAK, FAK and PDK family members, or PI(3) kinase or PI(3) kinase-related family members, and/or members of the cyclin-dependent kinase family (CDK) include those staurosporine derivatives disclosed in EP 0 296 110, *e.g.*, midostaurin; examples of further compounds include, *e.g.*, UCN-01, safingol, BAY 43-9006, Bryostatin 1; Ilmofosine; RO 318220 and RO 320432; GO 6976; Isis 3521; or LY333531/LY379196.

Further anti-angiogenic compounds include thalidomide (THALOMID™) and TNP-470.

Compounds which target, decrease or inhibit the activity of a protein or lipid phosphatasc include inhibitors of phosphatase 1, phosphatase 2A, PTEN or CDC25, *e.g.*, okadaic acid or a derivative thereof.

As used herein, cyclooxygenase inhibitor includes, but is not limited to, *e.g.*, celecoxib (Celebrex®), rofecoxib (Vioxx®), etoricoxib, valdecoxib or a 5-alkyl-2-arylaminophenylacetic acid, *e.g.*, 5-methyl-2-(2'-chloro-6'-fluoroanilino)phenyl acetic acid.

As used herein, "histone deacetylase inhibitor" includes, but is not limited to, MS-27-275, SAHA, pyroxamide, FR-901228 or valproic acid.

As used herein, "bisphosphonates" include, but are not limited to, etridonic, clodronic, tiludronic, pamidronic, alendronic, ibandronic, risedronic and zoledronic acid. Etridonic acid can be administered in the form as it is marketed under the trademark DIDRONEL™. Clodronic acid can be administered in the form as it is marketed under the trademark BONEFOS™. Tiludronic acid can be administered in the form as it is marketed under the trademark SKELID™. Pamidronic acid can be administered in the form as it is marketed under the trademark AREDIA™. Alendronic acid can be administered in the form as it is marketed under the trademark FOSAMAX™. Ibandronic acid can be

administered in the form as it is marketed under the trademark BONDRANAT™. Risedronic acid can be administered in the form as it is marketed under the trademark ACTONEL™. Zoledronic acid can be administered in the form as it is marketed under the trademark ZOMETA™.

As used herein, "matrix metalloproteinase inhibitor" includes, but is not limited to, collagen peptidomimetic and nonpetidomimetic inhibitors, tetracycline derivatives, *e.g.*, hydroxamate peptidomimetic inhibitor batimastat and its orally bioavailable analogue marimastat, prinomastat, BMS-279251, BAY 12-9566, TAA211 or AAJ996.

One of ordinary skill will appreciate that, from a medical practitioner's or patient's perspective, virtually any alleviation or prevention of an undesirable symptom associated with a cancerous condition (*e.g.*, pain, sensitivity, weight loss, and the like) would be desirable. Additionally, any reduction in tumor mass or growth rate is desirable, as well as an improvement in the histopathological picture of the tumor. Thus, for the purposes of this application, the terms "treatment", "therapeutic use", or "medicinal use" used herein shall refer to any and all uses of the claimed compositions which remedy a disease state or symptoms, or otherwise prevent, hinder, retard, or reverse the progression of disease or other undesirable symptoms in any way whatsoever.

An effective dosage and treatment protocol may be determined by conventional means, starting with a low dose in laboratory animals and then increasing the dosage while monitoring the effects, and systematically varying the dosage regimen as well. Animal studies, preferably mammalian studies, are commonly used to determine the maximal tolerable dose, or MTD, of bioactive agent per kilogram weight. Those skilled in the art regularly extrapolate doses for efficacy and avoiding toxicity to other species, including human.

Before human studies of efficacy are undertaken, Phase I clinical studies in normal subjects help establish safe doses. Numerous factors may be taken into consideration by a clinician when determining an optimal dosage for a given subject. Primary among these is the toxicity and half-life of the chosen conditional replication virus. Additional factors include the size of the patient, the age of the patient, the general condition of the patient, the particular cancerous disease being treated, the severity of the disease, the presence of other drugs in the patient, and the like. The trial dosages would be chosen after consideration of the results of animal studies and the clinical literature.

Where *in vivo* use is contemplated, the various biochemical components of the present invention are preferably of high purity and are substantially free of potentially

harmful contaminants (*e.g.*, at least National Food (NF) grade, generally at least analytical grade, and preferably at least pharmaceutical grade). To the extent that a given compound must be synthesized prior to use, such synthesis or subsequent purification shall preferably result in a product that is substantially free of any potentially toxic agents that may have been used during the synthesis or purification procedures.

For use in treating a cancerous condition in a subject, the present invention also provides in one of its aspects a kit or package, in the form of a sterile-filled container, vial or ampoule, that contains perifosine and a second chemotherapeutic agent. In one embodiment, the kit contains the above compounds in a suitable carrier or in any other stable form. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

The invention having been described, the following examples are offered by way of illustration and not limitation.

5. EXAMPLES

Perifosine is a member of the class of drugs called alkylphosphocholines. Amongst its mechanisms of action is the inhibition of Akt. In *in-vitro* experiments, the inhibition of Akt has been associated with increased apoptosis in non-small cell lung cancer cell lines. Further, perifosine has been shown to be non myelosuppressive. The major toxicity of perifosine has been gastrointestinal, mainly manifested as low grade nausea and vomiting or diarrhea.

The following studies will investigate the maximum tolerated dose and schedule of perifosine that can be administered without grade 3/4 gastrointestinal toxicity and without nausea or vomiting lasting for more than 48 hours beyond the last dose of perifosine in combination with certain other chemotherapeutic agents.

5.1 Determination of Tolerable and Acceptable Doses of Perifosine

The following section is a protocol for determining a tolerable and acceptable dose of perifosine with patients suffering from non-small cell lung cancer. Once the tolerable and acceptable dose is determined, perifosine is given at that dose to treat the non-small cell lung cancer.

In this study, a dose and schedule of perifosine that can be administered without grade 3/4 gastrointestinal toxicity and without nausea or vomiting lasting for more than 48 hours beyond the last dose of perifosine is defined as tolerable. The largest such dose will be defined as the acceptable dose and any dose beyond that as intolerable. These definitions are based on the assumption that this oral drug is well tolerated except for gastrointestinal toxicity and may need to be given for long periods of time.

In order to determine the most appropriate dosing regimen 4 different schedules of perifosine given weekly will be investigated. Three patients will be accrued at each dose level. All three patients will be observed for at least 1 week before subsequent dose escalation may proceed. The patients will be observed for this short time period because in prior phase I studies using these doses as a single oral dose or lower doses daily there have been no toxicities other than gastrointestinal and no life threatening toxicities of any type. If intolerable gastrointestinal toxicities are reported in 1/3 patients, the dose level will be expanded to 6 patients. If intolerable gastrointestinal toxicities are reported in ≤2/6 patients, then dose escalation will continue. If >2/6 patients experience intolerable gastrointestinal toxicity, the next lower dose will be considered the acceptable dose and will be expanded to 6 patients (if 6 patients were not already enrolled at that level). There will be no intra-patient dose escalations. Patients may continue to receive treatment until unacceptable toxicity or disease progression is encountered. The treatment regimens and dose levels outlined in the tables below will be used for dose escalation.

Dose Level	Unit Dose	Doses per week (q 6 hours)*	Cumulative dose/week
-1	250 mg	3	750 mg
1	300 mg	3	900 mg
2	300 mg	4	1200 mg
3	300 mg	5	1500 mg
4	300 mg	6	1800 mg

* The intervals between doses can be adjusted by the physician to suit the patient's lifestyle. For example a dose may be given up to 4 times a day during the patient's normal daily schedule.

TREATMENT PLAN

Perifosine Administration

Treatment will be administered weekly on an outpatient basis. Patients are to be instructed that all doses are to be taken with food. Patients will maintain a weekly patient

treatment diary to track doses of perifosine taken at home and return the diary to the clinic each week along with any remaining medication. The pills should remain intact and should not be split.

STUDY EVALUATIONS

	All assessments should be obtained prior to the first dose of perifosine in each week unless otherwise specified														
	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Off Study
Perifosine [a]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Informed consent	X														
Demographics	X														
Medical history	X	X		X		X				X				X	
Concurrent meds	X	X----------													
Physical exam	X	X	X	X		X				X				X[f]	X
Vital signs	X	X	X	X		X				X				X[f]	X
Height	X														
Weight	X		X	X		X				X				X[f]	
Performance status	X		X	X		X				X				X[f]	X
Serum Pregnancy Test[h]	X														
CBC w/diff, plts [b]	X		X			X				X				X[f]	X
Comprehensive Metabolic Panel [c,d]	X		X			X				X				X[f]	X
Glucose	X		X	X	X	X				X				X[f]	X
Adverse event evaluation	X	X----------													X
Patient Diary	X	X----------													X
Tumor measurements	X	Tumor measurements are repeated every *8 weeks*. Documentation (radiologic) must be provided for patients removed from study for progressive disease.													X[e]
Radiologic evaluation	X	Radiologic measurements should be performed every *8* weeks for the first 4 months and then every 12 weeks until disease progression.													X[e]
PK[g]		X[g]	X	X	X	X									

a: Perifosine: Dose/schedule as assigned.
b. Repeat weekly if ANC<1000, platelets < 50,000 or HgB < 10.
c: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT[AST], SGPT[ALT], sodium, uric acid, GGT.
d. Repeat weekly if patient experiences grade 2 vomiting or diarrhea
e: Off-study evaluation. It is preferable that two consecutive measurements taken 4 weeks apart be used to document progressive disease if the patient is removed from study for this reason.
f: Assessments to continue every 12 weeks while patients on study
g: PK samples to be drawn at pretreatment, 24h, 48h, after last dose of drug in week 1 and then one sample prior to the first dose in weeks 2, 3, 4 and 5 prior to taking medication for patients in part 1 of study only
h. Must be negative within 72 hours of treatment

History and physical examination will be taken (including weight and ECOG performance score) at each clinic visit, as well as height at the first visit. Patients will be seen and examined weekly for the first 3 weeks, week 5 and then at least once every 4 weeks. Patient will undergo imaging evaluation every 2 months for the first 4 months and every 3 months thereafter.

Once the tolerable and acceptable dose is determined, perifosine at that dose is then administered to the patients who have measurable disease for the treatment of non-small cell lung cancer.

5.2 Determination of More Favorable Dose

The following protocol is o determine the proportion of patients treated with perifosine at a dose of either 50 mg daily or 1200 mg weekly who experience a favorable outcome defined as at least one of the following: a complete or partial remission of the patient's disease by the RECIST criteria or a 50% increase in the time to progression compared to the treatment administered immediately prior to study entry. Patients must have histologically or cytologically confirmed diagnosis of either a lymphoma or solid tumor for which no standard therapy exists.

STUDY DESIGN

Treatment will be administered on an outpatient basis in 4 week cycles. Patients will receive perifosine orally daily (Arm A) or weekly (Arm B). Patients will be stratified by disease type and randomized to one of two treatment arms. On arm A patients will receive perifosine 50 mg/day. On arm B patients will receive perifosine 1200 mg/week.

TREATMENT PLAN

Arm A – Daily perifosine

Perifosine will be administered orally on an outpatient basis throughout the trial. The patient dose for daily administration will be 50 mg/day at bedtime. Patients are to be instructed that doses of perifosine are to be taken with food. Patients will maintain a weekly patient treatment diary to track doses of perifosine taken at home and return the diary to the clinic each week along with any remaining medication. The pills should remain intact and should not be split.

Daily Perifosine Administration (High Dose)

Perifosine will be administered orally on an outpatient basis throughout the trial. The patient dose for daily administration will be 150 mg/day taken in 3 doses at least 4 hours

apart. Patients are to be instructed that all doses of perifosine are to be taken with food. Patients will maintain a weekly patient treatment diary to track doses of perifosine taken at home and return the diary to the clinic each week along with any remaining medication. The pills should remain intact and should not be split.

Arm B – Weekly perifosine

Weekly Perifosine Administration (Initial Dose)

Perifosine will be administered orally on an outpatient basis throughout the trial. The patient dose will be 1200 mg/week. Patients are to be instructed that all doses of perifosine are to be taken with food. Patients will maintain a weekly patient treatment diary to track doses of perifosine taken at home and return the diary to the clinic each week along with any remaining medication. The pills should remain intact and should not be split. On the day perifosine is administered, the patient will receive anti-emetic pre-medication and 4 doses of 300 mg on one day. These doses should be given in the morning with food, with lunch, early afternoon with food and at bedtime. Patients should take no more than 300 mg perifosine at a time. The interval between doses of perifosine should be no less than 4 hours.

Weekly Perifosine Administration (Higher Dose)

Perifosine will be administered orally on an outpatient basis throughout the trial. The patient dose will be 1800 mg/week. Patients are to be instructed that all doses of perifosine are to be taken with food. Patients will maintain a weekly patient treatment diary to track doses of perifosine taken at home and return the diary to the clinic each week along with any remaining medication. The pills should remain intact and should not be split. On the day perifosine is administered, the patient will receive antiemetic pre-medication, 4 doses of 300 mg on day one and 2 doses on day 2. These doses should be given in the morning with food, with lunch, early afternoon with food and at bedtime. Patients should take no more than 300 mg perifosine at a time. The interval between doses of perifosine should be no less than 4 hours.

Duration of Treatment

All patients may continue therapy unless disease progression or dose limiting toxicity is documented.

STUDY EVALUATIONS

	All assessments should be obtained prior to the first dose of perifosine in each week unless otherwise specified														
	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13	Off Study[c]
Perifosine administration[a]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Informed consent	X														
Demographics	X														
Medical history	X	X----------													
Concurrent meds	X	X----------													
Physical exam	X	X	X			X				X				X[f]	
Vital signs	X	X	X			X				X				X[f]	
Height	X														
Weight	X	X	X			X				X				X[f]	
Performance status	X	X	X			X				X				X[f]	
CBC w/diff, plts	X													X[d]	
CBC			X			X				X				X[f]	
Serum chemistry[b]	X[d]													X[d]	
Serum pregnancy[e]	X														
Adverse event evaluation	X	X----------													X
Patient Diary	X	X----------													X
Tumor measurements	X	Tumor measurements are repeated every 12 weeks. Documentation (radiological) must be provided for patients removed from study for progressive disease.													X[c]
Radiologic evaluation	X	Radiologic measurements should be performed every 12 weeks													X[c]

a: Perifosine: Dose, route, schedule as assigned.
b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, uric acid, magnesium.
c: Off-study evaluation. It is preferable that two consecutive measurements taken to document progressive disease if the patient is removed from study for this reason.
d: Assessments to continue at least every 12 weeks while patient is on study.
e: Within 72 hours prior to initiation of therapy for women of childbearing potential only.
f: Assessments to continue at least every 4 weeks while patient is on study.

History and physical examination will be taken (including weight and ECOG performance score) at each clinic visit, as well as height at the first visit. Patients will be seen one week after they start on treatment, and examined at least every 4 weeks thereafter, at the discretion of the treating investigator. A CBC w/differential and serum chemistry will be performed every 12 weeks. Patients will undergo imaging evaluation every 12 weeks.

5.3 Co-administration of Perifosine and Paclitaxel

The following section is a protocol for determining the maximum tolerated dose (MTD) of perifosine that can be administered with paclitaxel. Patients must have histologically or cytologically confirmed diagnosis of cancer for which treatment with single agent paclitaxel would be an appropriate treatment option.

In this study the MTD is defined as a dose and schedule of perifosine that can be administered with paclitaxel without grade 3/4 non-hematologic toxicity. The largest such dose will be defined as the maximum tolerated dose and any dose beyond that as intolerable. The MTD will be determined for each arm separately.

Study Description

Patients on Arm A will receive perifosine orally on days 1-21 of each 28 day cycle. Paclitaxel, 80 mg/m^2, will be administered intravenously over 1 hour on days 1, 8 and 15 of a 28 day cycle.

Patients on Arm B will receive perifosine orally on days 1-14 of each 21 day cycle. Paclitaxel, 175 mg/m^2, will be administered intravenously over 1 hour on day 8 of a 21 day cycle.

Patients on both arms of the study will receive pre-medication around the time of paclitaxel administration in a manner consistent with current labeling, as described below.

Three different dose-schedules of perifosine will be investigated. The first 3 patients at each perifosine dose level will be accrued on arm A and the next 3 patients will be accrued on arm B. On each arm all three patients will be observed for at least 1 cycle (28 and 21 days respectively) before subsequent dose escalation may proceed on that arm. Patients may be accrued to the alternate arm during this observation period providing all other criteria for escalation are met.

For each arm, if grade 3/4 non-hematologic toxicities are reported in 2/3 patients, the dose level for that arm will be expanded to 6 patients. If grade 3/4 non-hematologic toxicities are reported in $\leq$ 3/6 patients, then dose escalation for that arm will continue. If >3/6 patients experience grade 3/4 non-hematologic toxicity, the next lower dose will be considered the maximum tolerated dose for that arm. If 6 patients were not already treated at that dose level, it will be expanded to 6 patients. There will be no intra-patient dose escalations. Patients may continue to receive treatment until unacceptable toxicity or disease progression is encountered.

The dose levels of perifosine outlined in the tables below will be used for dose escalation.

Dose Level	Perifosine Doses per day	Cumulative dose/day
1	1	50 mg
2	2	100 mg
3	3	150 mg

For each arm, if after dose level 3 the maximum tolerated dose has not been reached then dose escalation will be halted.

TREATMENT PLAN

Perifosine will be administered orally on an outpatient basis. On Arm A perifosine will be taken on days 1-21 of each cycle. On Arm B perifosine will be taken on days 1-14 of each cycle. The patient dose will be determined at the time of registration, according to the algorithm outlined in section 4.2. No investigational or commercial agents or therapies other than those described in this protocol may be administered with the intent to treat the patient's malignancy.

Patients are to be instructed that all doses of perifosine are to be taken with food. Patients will maintain a weekly patient treatment diary to track doses of perifosine taken at home and adverse events experienced, and return the diary to the clinic at each visit along with any remaining medication. The pills should remain intact and should not be split.

When a patient is receiving a single dose of perifosine it should be given at bedtime. If 2 doses are given, one should be given in the morning with food and the other at bedtime. If 3 doses per day are given, they should be given in the morning with food, early afternoon with food and at bedtime. The interval between doses of perifosine should be no less than 4 hours.

Paclitaxel

On Arm A paclitaxel 80 mg/m^2 will be administered intravenously over 1 hour on days 1, 8 and 15 of each 28-day cycle.

On Arm B paclitaxel 175 mg/m^2 administered on day 8 of a 21-day cycle. Since the patient will already be at a steady state level of perifosine the exact timing of perifosine relative to paclitaxel will be at the discretion of the investigator.

Paclitaxel Premedication

Patients on both arm A and arm B will receive pre-medication to include diphenhydramine 50 mg, ranitidine 50 mg and dexamethasone 20 mg all by IV at 30 minutes prior to treatment.

This pre-medication regimen is described as acceptable in the latest edition of the paclitaxel package insert.

STUDY EVALUATIONS

ARM A	All assessments should be obtained prior to the first dose of perifosine in each week unless otherwise specified													
	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Off Study[c]
Perifosine administration[a]		X	X	X		X	X	X		X	X	X		
Paclitaxel administration			X	X		X	X	X		X	X	X		
Informed consent	X													
Demographics	X													
Medical history	X	X----------												
Concurrent meds	X	X----------												
Physical exam	X	X	X	X		X				X[d]				
Vital signs	X	X	X	X		X	X	X		X	X	X[e]		
Height	X													
Weight	X	X	X	X		X	X	X		X	X	X[e]		
Performance status	X	X	X	X		X	X	X		X	X	X[e]		
CBC w/diff, plts	X	X	X	X		X	X	X		X	X	X[e]		
Serum chemistry[b]	X	X	X	X		X				X[d]				
Serum pregnancy[f]	X													
Adverse event evaluation	X	X ----------												X
Patient Diary	X	X ----------												X
Tumor measurements	X	Tumor measurements are repeated every 9 *weeks*. Documentation (radiological) must be provided for patients removed from study for progressive disease.												X[c]
Radiologic evaluation	X	Radiologic measurements should be performed every 9 *weeks*												X[c]

a: Perifosine: Dose, route/schedule as assigned.
b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, uric acid, magnesium.
c: Off-study evaluation. It is preferable that two consecutive measurements taken 4 weeks apart be used to document progressive disease if the patient is removed from study for this reason.
d: Assessments to continue weeks 1 of each cycle while patients on study.
e: Assessments to continue weeks 1, 2 and 3 of each cycle while patients on study.
f: Within 72 hours prior to initiation of therapy for women of childbearing potential only.

Arm B	All assessments should be obtained prior to the first dose of perifosine in each week unless otherwise specified															
	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13[d]	Wk 14[d]	Off Study[c]
Perifosine administration[a]		X	X		X	X		X	X		X	X		X	X	
Paclitaxel administration			X			X			X			X			X	
Informed consent	X															
Demographics	X															
Medical history	X	X----------														
Concurrent meds	X	X----------														
Physical exam	X	X	X		X	X			X			X			X[d]	
Vital signs	X	X	X		X	X		X	X		X	X		X	X[e]	
Height	X															
Weight	X	X	X		X	X		X	X		X	X		X	X[e]	
Performance status	X	X	X		X	X		X	X		X	X		X	X[e]	
CBC w/diff, plts	X		X		X	X		X	X		X	X		X	X[e]	
Serum chemistry[b]	X		X			X			X			X			X[d]	
Serum pregnancy[f]	X															
Adverse event evaluation	X	X ----------														X
Patient Diary	X	X ----------														X
Tumor measurements	X	Tumor measurements are repeated every 9 *weeks*. Documentation (radiological) must be provided for patients removed from study for progressive disease.														X[c]
Radiologic evaluation	X	Radiologic measurements should be performed every 9 weeks														X[c]

a: Perifosine: Dose, route/schedule as assigned.
b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, uric acid, magnesium.
c: Off-study evaluation. It is preferable that two consecutive measurements taken 4 weeks apart be used to document progressive disease if the patient is removed from study for this reason.
d: Assessments to continue on week 2 of each cycle while patients on study.
e: Assessments to continue on weeks 1 and 2 of each cycle while patients on study.
f: Within 72 hours prior to initiation of therapy for women of childbearing potential only.

History and physical examination will be taken (including weight and ECOG performance score) at each clinic visit, as well as height at the first visit. On Arm A patients will be seen and examined on weeks 1, 2 and 3 of each cycle. On Arm B patients

will be seen and examined on weeks 1 and 2 of each cycle. Patients will undergo imaging evaluation every 9 weeks for the first 3 months and every 3 months thereafter.

5.4 Co-administration of Perifosine and Docetaxel, with or without Prednisone

The following section is a protocol for determining the maximum tolerated dose (MTD) of perifosine that can be administered with docetaxel. Patients must have histologically or cytologically confirmed diagnosis of cancer for which treatment with single agent docetaxel would be an appropriate treatment option.

In this study the MTD is defined as a dose and schedule of perifosine that can be administered with docetaxel with or without prednisone without grade 3/4 non-hematologic toxicity. The largest such dose will be defined as the maximum tolerated dose and any dose beyond that as intolerable.

Study Description

Part 1

Docetaxel 75 mg/m^2 on day 8 will be administered every 21 days. Docetaxel will be administered intravenously over 1 hour. On arm A docetaxel only will be given with perifosine. On arm B all patients will receive prednisone 5 mg bid on a continuous basis beginning on the first day of perifosine.

Three different schedules of perifosine given weekly will be investigated. The first 3 patients at each perifosine dose level will be accrued on arm A and the next 3 patients will be accrued on arm B. On each arm all three patients will be observed for at least 1 cycle before subsequent dose escalation may proceed on that arm. Patients may be accrued to the alternate arm during this observation period providing all other criteria for escalation are met. Patients will receive perifosine on days 1-14 of each 21 day cycle.

For each arm, if grade 3/4 non-hematologic toxicities are reported in 2/3 patients, the dose level for that arm will be expanded to 6 patients. If grade 3/4 non-hematologic toxicities are reported in $\leq$ 3/6 patients, then dose escalation for that arm will continue. If >3/6 patients experience grade 3/4 non-hematologic toxicity, the next lower dose will be considered the maximum tolerated dose for that arm. If 6 patients were not already treated at that dose level, it will be expanded to 6 patients. There will be no intra-patient dose escalations. Patients may continue to receive treatment until unacceptable toxicity or disease progression is encountered. The dose levels of perifosine outlined in the tables below will be used for dose escalation.

Dose Level	Perifosine Doses per day	Cumulative dose/day
1	1	50 mg
2	2	100 mg
3	3	150 mg

For each arm, if after dose level 3 the maximum tolerated dose has not been reached then dose escalation will be halted.

While arm B includes an additional drug – prednisone – the reported toxicity of the combination is lower than single agent docetaxel. Thus, escalation on arm B may continue even if grade 3/4 non-hematologic toxicity has been observed at the same dose level without prednisone.

Part 2

In part 2 of the study, 10 patients each will be treated with the maximum tolerated dose of perifosine identified according to the protocol above.

Perifosine will be administered days 1-14 of each cycle on an outpatient basis. The MTD patient dose will be determined as outlined above.

On day 8 of each cycle when perifosine is administered with docetaxel, the first dose of perifosine will be administered immediately after the docetaxel.

Patients are to be instructed that all doses of perifosine are to be taken with food. Patients will maintain a weekly patient treatment diary to track doses of perifosine taken at home and return the diary to the clinic each week along with any remaining medication. The pills should remain intact and should not be split.

All patients will receive dexamethasone 8 mg po at 12 hours, 3 hours and 1 hour prior to docetaxel administration to minimize the likelihood of an anaphylactic reaction or fluid retention.

Docctaxel 75 mg/m^2 will be administered over 1 hour on day 8 of each 21-day cycle.

Prednisone 5 mg bid will be given continuously beginning on day 1 of perifosine administration to patients in arm B only.

STUDY EVALUATIONS

	All assessments should be obtained prior to the first dose of perifosine in each week unless otherwise specified															
	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13[d]	Wk 14[d]	Off Study[c]
Perifosine [a]		X	X		X	X		X	X		X	X		X	X	
Docetaxel			X			X			X			X			X	
Prednisone (Arm B only)		X----------														
Informed consent	X															
Demographics	X															
Medical history	X	X----------														
Concurrent meds	X	X----------														
Physical exam	X	X	X		X	X		X	X		X	X		X[d]	X[d]	
Vital signs	X	X	X		X	X		X	X		X	X		X[d]	X[d]	
Height	X															
Weight	X	X	X		X	X		X	X		X	X		X[d]	X[d]	
Performance status	X	X	X		X	X		X	X		X	X		X[d]	X[d]	
CBC w/diff, plts	X		X	X		X	X		X	X		X	X		X	
Serum chemistry [b]	X		X			X			X			X			X	
Serum pregnancy [f]	X															
Glucose	X		X	X		X			X			X			X	
Adverse event evaluation	X	X----------														X
Patient Diary	X	X----------														X
Tumor measurements	X	Tumor measurements are repeated every *6weeks.* Documentation (radiological) must be provided for patients removed from study for progressive disease.														X[c]
Radiologic evaluation	X	Radiologic measurements should be performed every *6* weeks for the first 3 months and then every 9 weeks.														X[c]

a: Perifosine: Dose, route/schedule as assigned.
b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, uric acid, magnesium.
c: Off-study evaluation. It is preferable that two consecutive measurements taken 4 weeks apart be used to document progressive disease if the patient is removed from study for this reason.
d: Assessments to continue every 3 weeks while patients on study
e: Assessments to continue weeks 1 and 2 of each cycle while patients on study
f: Assessments to continue every 12 weeks while patients on study
g: Within 72 hours prior to initiation of therapy for women of childbearing potential only

History and physical examination will be taken (including weight and ECOG performance score) at each clinic visit, as well as height at the first visit. Patients will be seen and examined weekly in weeks 1 and 2 of each cycle. Patient will undergo imaging evaluation every 6 weeks for the first 3 months and every 3 months thereafter.

5.5 Co-Administration of Perifosine and Gemcitabine

The following section is a protocol for determining the maximum tolerated dose (MTD) of perifosine that can be administered with gemcitabine. In this study the MTD is defined as a dose and schedule of perifosine that can be administered with gemcitabine without grade 3/4 non-hematologic toxicity. The largest such dose will be defined as the maximum tolerated dose and any dose beyond that as intolerable.

Study Description

Part 1

Gemcitabine 1000 mg/m^2 days 1, 8 administered every 21 days. Gemcitabine will be administered intravenously over 30 minutes.

Three different schedules of perifosine given weekly will be investigated. Three patients will be accrued at each dose level. All three patients will be observed for at least 1 cycle before subsequent dose escalation may proceed. Patients will receive perifosine on days 1-14 of each 21day cycle.

If grade 3/4 non-hematologic toxicities are reported in 2/3 patients, the dose level will be expanded to 6 patients. If grade 3/4 non-hematologic toxicities are reported in ≤ 3/6 patients, then dose escalation will continue. If >3/6 patients experience grade 3/4 non-hematologic toxicity, the next lower dose will be considered the maximum tolerated dose and will be expanded to 6 patients (if 6 patients were not already enrolled at that level). There will be no intra-patient dose escalations. Patients may continue to receive treatment until unacceptable toxicity or disease progression is encountered. The treatment regimens and dose levels outlined in the tables below will be used for dose escalation.

Dose Level	Perifosine Doses per day	Cumulative dose/day
1	1	50 mg
2	2	100 mg
3	3	150 mg

If after dose level 3 the maximum tolerated dose has not been reached then dose escalation will be halted.

Part 2

In part 2 of the study, 10 patients will be treated with the maximum tolerated dose of Gemcitabine identified by the protocol above.

In cycle 1 the perifosine will begin on day 2 to accommodate pharmacokinetic sampling. The remainder of the cycles the perifosine will be administered as described below.

On days 1 and 8 of each cycle when perifosine is administered with gemcitabine, perifosine will be administered immediately after the gemcitabine.

Treatment will be administered days 1-14 of each cycle on an outpatient basis.

Patients are to be instructed that all doses of perifosine are to be taken with food. Patients will maintain a weekly patient treatment diary to track doses of perifosine taken at home and return the diary to the clinic each week along with any remaining medication. The pills should remain intact and should not be split.

Gemcitabine 1000 mg/m2 will be administered over 30 minutes on day 1 and day 8 of each 21-day cycle.

STUDY EVALUATIONS

	All assessments should be obtained prior to the first dose of perifosine in each week unless otherwise specified													
	Pre-Study	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12	Wk 13[d]	Off Study[e]
Perifosine [a]		X	X		X	X		X	X		X	X		X	
Gemcitabine		X	X		X	X		X	X		X	X		X	
Informed consent	X														
Demographics	X														
Medical history	X	X			X			X			X			X	
Concurrent meds	X	X----------													
Physical exam	X	X	X		X	X		X			X			X[d]	
Vital signs	X	X	X		X	X		X			X			X[d]	
Height	X														
Weight		X	X		X	X		X	X		X	X		X[d]	
Performance status	X	X	X		X	X		X	X		X	X		X[d]	
CBC w/diff, plts	X	X	X		X	X		X	X		X	X		X[e]	
Serum chemistry [b]	X	X	X		X	X		X	X		X	X		X	
Serum pregnancy[g]	X														
Glucose	X	X			X	X		X	X		X			X	
Adverse event evaluation	X	X----------													X
Patient Diary	X	X----------													X
Tumor measurements	X	Tumor measurements are repeated every 6*weeks*. Documentation (radiologic) must be provided for patients removed from study for progressive disease.													X[c]
Radiologic evaluation	X	Radiologic measurements should be performed every 6 weeks for the first 3 months and then every 9 weeks.													X[c]
PK[f]		X[f]	X												

a: Perifosine: Dose, route/schedule as assigned.
b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT[AST], SGPT[ALT], sodium, uric acid, magnesium.
c: Off-study evaluation. It is preferable that two consecutive measurements taken 4 weeks apart be used to document progressive disease if the patient is removed from study for this reason.
d: Assessments to continue every 3 weeks while patients on study
e: Assessments to continue weeks 1 and 2 of each cycle while patients on study
e: Assessments to continue every 12 weeks while patients on study
f: PK samples will be drawn on C1D1,C1D 8-9, C1 D15. See section 5.6 for times
g: Within 72 hours prior to initiation of therapy

History and physical examination will be taken (including weight and ECOG performance score) at each clinic visit, as well as height at the first visit. Patients will be

seen and examined weekly in weeks 1 and 2, weeks 3 and 4 and then at least once every 3 weeks. Patient will undergo imaging evaluation every 6 weeks for the first 3 months and every 3 months thereafter.

5.6 Co-Administration of Perifosine and Trastuzumab

The following section is a protocol for treating patients with cancer with perifosine and trastuzumab. Patients must have histologically or cytologically confirmed diagnosis of metastatic breast cancer that is HER2/neu positive by FISH or 3+ positive by immunohistochemistry.

STUDY DESIGN

Treatment will be administered on an outpatient basis. Patients will receive perifosine orally during a 1 week lead-in period, and over a 21 day cycle. All patients will receive trastuzumab at a dose of 6 mg/kg on day 1 of a 21 day cycle. The infusion rate will be determined according to patient's previous experience with trastuzumab infusions. Patients will be stratified by the number of prior trastuzumab containing regimens they have received and randomized to one of three treatment arms. On arm A patients will receive perifosine 50 mg/day. On arm B patients will receive perifosine 50 mg tid. On arm C patients will receive 900 mg weekly.

Perifosine will be administered orally on an outpatient basis throughout the trial. The patient dose will be 50 mg/day or 50 mg bid or 900 mg weekly according to their randomization at registration.

Patients are to be instructed that all doses of perifosine are to be taken with food. Patients will maintain a weekly patient treatment diary to track doses of perifosine taken at home and return the diary to the clinic each week along with any remaining medication. The pills should remain intact and should not be split.

When 900 mg of perifosine are administered weekly, the patient will receive antiemetic premedication, and 3 doses of 300 mg on one day.

When a patient is receiving a single dose of perifosine it should be given at bedtime. When 3 doses per day are given, they should be given in the morning with food, early afternoon with food and at bedtime. The interval between doses of perifosine should be no less than 4 hours.

Trastuzumab will be administered intravenously on day 1 of a 21 day cycle at a dose of 6 mg/kg. Since these patients have already received trastuzumab, the infusion rate should be according to their previous experience. Since the patient will already be at a

steady state level of perifosine, the exact timing of perifosine relative to trastuzumab will be at the discretion of the investigator.

All patients may continue therapy unless disease progression or dose limiting toxicity is documented.

STUDY EVALUATIONS

	All assessments should be obtained prior to the first dose of perifosine in each week unless otherwise specified													
	Pre-Study	Wk 0	Wk 1	Wk 2	Wk 3	Wk 4	Wk 5	Wk 6	Wk 7	Wk 8	Wk 9	Wk 10	Wk 11	Wk 12[d]	Off Study[c]
Perifosine administration[a]		X	X	X	X	X	X	X	X	X	X	X	X	X	
Trastuzumab administration			X			X			X			X[d]			
Informed consent	X														
Demographics	X														
Medical history	X	X----------													
Concurrent meds	X	X----------													
Physical exam	X	X	X		X	X			X			X[d]			
Vital signs	X	X	X		X	X			X			X[d]			
Height	X														
Weight	X	X	X		X	X			X			X[d]			
Performance status	X	X	X		X	X			X			X[d]			
CBC w/diff, plts	X		X		X	X			X			X[d]			
Serum chemistry[b]	X		X			X			X			X[d]			
Serum pregnancy[e]	X														
Adverse event evaluation	X	X ----------													X
Patient Diary	X	X ----------													X
Tumor measurements	X	Tumor measurements are repeated every 9 weeks. Documentation (radiological) must be provided for patients removed from study for progressive disease.													X[c]
Radiologic evaluation	X	Radiologic measurements should be performed every 9 weeks													X[c]

a: Perifosine: Dose, route, schedule as assigned.
b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, uric acid, magnesium.
c: Off-study evaluation. It is preferable that two consecutive measurements taken to document progressive disease if the patient is removed from study for this reason.
d: Assessments to continue on week 1 of each cycle while patient is on study.
e: Within 72 hours prior to initiation of therapy for women of childbearing potential only.

History and physical examination will be taken (including weight and ECOG performance score) at each clinic visit, as well as height at the first visit. Patients will be seen and examined weekly in week 0, and on day 1 of each cycle, or more, at the discretion of the treating investigator. Patients will undergo imaging evaluation every 9 weeks for the first 3 months and every 3 months thereafter.

6. REFERENCES CITED

Many modifications and variations of this invention can be made without departing from its spirit and scope, as will be apparent to those skilled in the art. The specific embodiments described herein are offered by way of example only, and the invention is to be limited only by the terms of the appended claims, along with the full scope of equivalents to which such claims are entitled. Such modifications are intended to fall within the scope of the appended claims.

All references, patent and non-patent, cited herein are incorporated herein by reference in their entireties and for all purposes to the same extent as if each individual publication or patent or patent application was specifically and individually indicated to be incorporated by reference in its entirety for all purposes.

WHAT IS CLAIMED IS:

1. A method for treating solid tumors in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of perifosine and a second chemotherapeutic agent.

2. A method for inhibiting growth of solid tumors in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of perifosine and a second chemotherapeutic agent.

3. A method for inducing tumor regression in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of perifosine and a second chemotherapeutic agent.

4. A method for treating solid tumor invasiveness or symptoms associated with such tumor growth or invasiveness in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of perifosine and a second chemotherapeutic agent.

5. A method for preventing metastatic spread of tumors or for preventing or inhibiting growth of micro-metastases in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of perifosine and a second chemotherapeutic agent.

6. A method for the treatment of a disease associated with deregulated angiogenesis in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of perifosine and a second chemotherapeutic agent.

7. A method for inhibiting or controlling deregulated angiogenesis in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of perifosine and a second chemotherapeutic agent.

8. A method for enhancing the activity of a chemotherapeutic agent or for overcoming resistance to a chemotherapeutic agent in a subject in need thereof, comprising administering to said subject a therapeutically effective amount of perifosine and a second chemotherapeutic agent, either concomitantly or sequentially with said chemotherapeutic agent.

9. A method for treating post-transplant lymphoproliferative disorders or a lymphatic cancer in a subject in need thereof, comprising co-administering to said subject, concomitantly or in sequence, perifosine and a second chemotherapeutic agent.

10. The method according to claim 1-9, wherein the second chemotherapeutic agent is selected from the group consisting of paclitaxel, docetaxel, gemcitabine and trastuzumab.

11. Use of a perifosine and a second chemotherapeutic agent for the manufacture of a medicament for treating or preventing solid tumors.

12. Use of perifosine and a second chemotherapeutic agent for the manufacture of a medicament for treating solid tumor invasiveness.

13. Use of perifosine and a second chemotherapeutic agent for the manufacture of a medicament for the treatment of a disease associated with deregulated angiogenesis.